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Highly enantioselective hetero Diels–Alder reactions of N-sulfinyl dienophiles promoted by copper(II)- and zinc(II)-chiral bis(oxazoline) complexes

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Abstract—Hetero Diels–Alder reactions of 1,3-cyclohexadiene with *N*-sulfinyl dienophiles **1a** or **1b**, promoted by Cu(II)- or Zn(II)-chiral bis(oxazoline) complexes, afforded *endo* adducts in high yields (up to 85%) and enantiomeric excess (e.e. of up to >98%) under stoichiometric conditions. With 10 mol% loading of the Zn(II) catalyst up to 75% e.e. was obtained for the *endo* adduct (*endo:exo*=10:1, total yield 68%). © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Hetero Diels–Alder (HDA) reactions of *N*-sulfinylaniline to conjugated dienes were first described by Wichterle and Roceck in 1953.¹ Since then a number of Diels–Alder reactions for various types of *N*-sulfinyl compounds have been reported.^{2,3} The resulting heterocyclic products can be further transformed into synthetically useful derivatives, e.g. homoallylic amines and vicinal amino alcohols, by well established techniques.^{2f}

Recently, we described the first enantioselective HDA reaction of *N*-sulfinyl dienophiles with 1,3-cyclohexadiene promoted by stoichiometric amounts of chiral titanium catalysts.⁴ The *endo* adducts were typically obtained in 50–80% yield with 36–76% e.e. The moderate stereoselectivities and the time consuming method for preparation of the titanium catalysts, initiated us to screen several chiral Lewis acids. Herein, we present our preliminary findings applying the known chiral bis(oxazoline)-metal complexes $3a-c^5$ as Lewis acid catalysts (Table 1).

2. Results and discussion

2.1. Stoichiometric reactions

In general, excellent *endo/exo* selectivities (>95:<5) were

observed when stoichiometric amounts of 3a-c were applied in the reactions of the N-sulfinyl compounds $1\hat{a}^6$ or $1b^{2b}$ with 1,3-cyclohexadiene (Table 1). The best enantioselectivities, >98% e.e. for 1b (X = Ts, entries 8 and 11), were obtained with the Lewis acids 3a [M = $Cu(OTf)_2$ and $3c [M = Zn(OTf)_2]$. These reactions gave the endo adduct of **2b** (X = Ts) with (1R,2S,4S)configuration⁴ in 85 and 83% yield, respectively. The same catalysts converted the Cbz dienophile 1a (entries 2 and 6) to endo adduct 2a in 92 and 90% e.e. Cycloadduct 2a had the same absolute configuration as 2b, indicating that 1a and 1b complex in a similar manner with the chiral Lewis acids involved. A decrease in e.e. was noted when the counterion of the Cu(II) complex was changed from OTf (3a) to the less associating SbF_6 (3b),⁷ as shown in entries 1 and 4 for N-sulfinyl 1a, and entries 8 and 10 for 1b. A significant increase in e.e. was observed for 1a on lowering the reaction temperature from -55 to -85° C, and using the Lewis acids **3a** or **3c**. At -55°C the e.e.s observed using 3a and 3c were 78 and 67%, respectively, whereas at -85°C e.e.s of 92 and 90% were achieved (entries 1, 2, 5, and 6). The temperature had no effect on the d.e. (endo/exo > 95:<5) or the yield of the products (62-68%).

2.2. Catalytic reactions

Attempts to perform the reaction with catalytic amounts of the Lewis acid $3a [M = Cu(OTf)_2]$ gave rather disappointing results. A distinct drop in d.e. and

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Table 1. Asymmetric Diels-Alder reactions of N-sulfinyl dienophiles 1a and 1b with 1,3-cyclohexadiene promoted by chiralbis(oxazoline)-Cu(II) (3a and 3b) and -Zn(II) (3c) Lewis acids



Entry	Dienophile	Catalyst (mol%)	Temp. °C (time, h)	Yield ^a (%)	$endo/exo^{b}$	% e.e. ^c (config. <i>endo</i> -2) ^d
1	1a	3a (100)	-55 (22)	66	>95:<5	78 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)
2	1a	3a (100)	-85 (22)	63	>95:<5	92 $(1R, 2S, 4S)$
3	1a	3a (10)	-55 (22)	25	38:62	15(1R,2S,4S)
4	1a	3b (100)	-55 (22)	50	>95:<5	30 (1R, 2S, 4S)
5	1a	3c (100)	-55 (22)	62	>95:<5	67 (1R, 2S, 4S)
6	1a	3c (100)	-85 (22)	68	>95:<5	90 (1R, 2S, 4S)
7	1a	3c (10)	-60(24)	44	81:19	61 (1R, 2S, 4S)
8	1b	3a (100)	-85 (14)	85	>95:<5	>98 (1R, 2S, 4S)
9	1b	3a (10)	-85 (24)	93	82:18	36(1R,2S,4S)
10	1b	3b (100)	-85 (14)	68	>95:<5	43 (1R, 2S, 4S)
11	1b	3c (100)	-85 (22)	83	>95:<5	>98 (1R, 2S, 4S)
12	1b	3c (10)	-85 (22)	68	10:1	75 (1 <i>R</i> ,2 <i>S</i> ,4 <i>S</i>)

^a Isolated yield of *endo*- and *exo*-2.

^b Determined by ¹H NMR (400 MHz) on the crude product.

^c Determined by chiral HPLC.⁴

^d Absolute configuration was established by chemical correlation.⁴

e.e. was observed in reactions with 10 mol% loading of **3a** (entries 3 and 9 for *N*-sulfinyl **1a** and **1b**, respectively). This observation indicates that the catalyst is not released from the HDA adducts, thus inhibiting catalyst turnover. The high yield observed in the reaction with the Ts dienophile **1b** (93%, entry 9) may be explained by a pronounced background reaction. The uncatalysed reaction at -85° C (reaction time 17 h) gave a 55% yield of product (*endo/exo*=64:36). For the Cbz dienophile **1a**, the uncatalysed reaction gave 17% yield (*endo/exo*=14:86) at -55° C after 24 h.

The results obtained with the copper complex **3a** prompted us to look for a catalyst that might be released more easily from the HDA products. Since Zn(II) complexes are weaker Lewis acids than the corresponding Cu(II) complexes,^{8a} the zinc complex **3c** was tested on our systems. The reaction using the Cbz dienophile **1a** and 10 mol% of the zinc complex **3c** (entry 7) gave only a slight decrease in the e.e., but the *endo/exo* ratio and the yield were lower compared to entry 5. The same general picture was found for the Ts dienophile **1b**. However, the e.e. decreased from >98% in the stoichiometric case to 75% in the catalytic reaction (see entries 11 and 12). Although the results obtained with the zinc complex **3c** were not optimal, we regard them as promising leads in our continuing

search for efficient catalysts for HDA reactions involving *N*-sulfinyl dienophiles.

The postulated intermediate presented in Fig. 1 is based on the assumption that the *N*-sulfinyl dienophiles **1a** or **1b** (last compound is not shown) engage in bidentate coordination to the chiral Lewis acid with the *N*-sulfinyl oxygen and the carbonyl oxygen or one of the sulfonyl oxygens, respectively. A tetrahedral metal centre explains the stereochemical outcome of the reactions shown in Table 1. While the possibility of tetrahedral geometry for Cu(II) complexes has been the subject of some debate,⁹⁻¹³ tetrahedral metal centres are well known for Zn(II) complexes.^{8,14}

In summary, highly enantioselective HDA reactions of N-sulfinyl dienophiles with 1,3-cyclohexadiene have



Figure 1. Postulated intermediate with tetrahedral arrangement.

been performed in the presence of stoichiometric amounts of Cu(II)- and Zn(II)-chiral bis(oxazoline) complexes. Attempts with catalytic amounts of Lewis acid were most promising for the Zn(II) complex. Further efforts to find catalysts offering an increased turnover and high enantioselectivities, as well as studies of the scope and limitation of these reactions in general are now in progress.

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